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The Acid-Catalyzed Cyclizations of Unsaturated Carbonyl Compounds Utilizing Silica Gel at High Pressure

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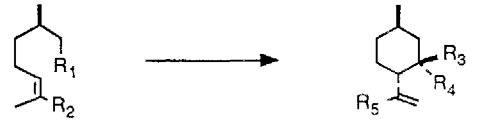
Abstract: The ene-like cyclizations of a series of unsaturated carbonyl compounds have been studied using silica gel at high pressure (15 kbar) as a new catalytic system. This new method is general for forming 5- and 6-membered ring carbocycles. The mildness of this method was demonstrated by the successful cyclization of a vinyl cyclopropyl aldehyde.

The acid-catalyzed intramolecular cyclization of unsaturated carbonyl compounds is a reaction which has been studied in great detail.[1] It is particularly attractive for synthesis because functionality is maintained on both sides of the new carbon-carbon bond. Although the Lewis acid-catalyzed cyclization of unsaturated carbonyl compounds has been shown to be of general synthetic utility, a wide variety of the Lewis acids typically used are not compatible with highly sensitive functionality often found in complex synthetic targets. Several reports in the literature have indicated that silica gel may be an effective catalyst for the cyclization of unsaturated carbonyl compounds (see below).[2a,b] The development of a general carbonyl-olefin cyclization method employing silica gel as the only acid source would certainly be of great value. In an effort to further expand the scope and limitations of using silica gel as a mild acid catalyst, the cyclizations of a variety of unsaturated carbonyl compounds have been investigated using silica gel at high pressure (15 kbar) as the catalytic system.

The ability of high pressure to lower the pKa of both organic and inorganic acids has been documented.[3] Although the effect of high pressure on the acidity of silica gel[4] is unknown, the results obtained with a variety of inorganic acids supports the hypothesis that silica gel will become a stronger acid at higher pressures. Since the acid-catalyzed cyclization of unsaturated carbonyl compounds involves both bond formation and charge development in the transition state, high pressure should also greatly increase the rate of cyclization.[5] The suppression of bond cleavage reactions at high pressure should facilitate the isolation of sensitive alcoholic products that could readily dehydrate under more standard conditions.

The unsaturated carbonyl 6-ring precursors that were studied in the presence of SiO_2 at 15 kbar[6-8] are presented in Table I. The SiO_2/high pressure promoted cyclizations of **1**, **3**, and **4**[9] gave yields of cyclized products that were comparable to previously published methods using Me_2AlCl[2c] and $ZnBr_2$.[10] Since methyl ketone **3** was less reactive than aldehyde **1**, a similar yield of cyclized product **7** required a higher reaction temperature. Aldehyde **2** displayed significantly diminished reactivity towards cyclization, even when exposed to forcing SiO_2/high pressure conditions. The use of Me_2AlCl has been reported to give a 90% yield of **6b**,[2c] indicating that the Lewis acidity of SiO_2 at 15 kbar may be slightly less than that of Me_2AlCl.

Table I: 6-Ring Cyclizations Using Oven-dried Silica Gel at 15 kbar.



starting cmpd		products			yield	conditions
R_1	R_2	R_3	R_4	R_5	(%)	
1: CHO	CH_3	**5a**: OH	H	CH_3	58	SiO_2, CH_2Cl_2, 15 kbar, 48 h, 25 °C
		5b: H	OH	CH_3	15	no **1** remained
2: CHO	H	**6a**: OH	H	H	5	SiO_2, CH_2Cl_2, 15 kbar, 48 h, 60 °C
		6b: H	OH	H	20	52% unreacted **2** isolated
3: COMe	CH_3	**7a**: OH	CH_3	CH_3	46	SiO_2, CH_2Cl_2, 15 kbar, 48 h, 50 °C
		7b: CH_3	OH	CH_3	20	30% unreacted **3** isolated
4: $CH{=}C(CO_2Me)_2$	CH_3	**8a**: $CH(CO_2Me)_2$	H	CH_3	66	SiO_2, CH_2Cl_2, 15 kbar, 90 min, 25 °C
		8b: H	$CH(CO_2Me)_2$	CH_3	7	25% unreacted **4** isolated

Although the product stereoselectivities in the cyclizations of **1** and **4** were similar to published data,[2c,10] the selectivity for **7a** and **7b** was opposite to that obtained in the Me_2AlCl catalyzed cyclization of **3**.[2c] A possible explanation for the observed reversal of selectivity in the silica gel-catalyzed reaction may be obtained from an examination of the transition states involved (Fig. 1). Since a proton is the most likely acid available with the silica gel catalyst, transition state **II** should be favored over transition state **I** by ~1 kcal mol^{-1} based on the developing A(1,3) interaction in transition state I.[11] The complex with Me_2AlCl may be sufficiently bulky that the interaction in transition state **II** becomes dominating, thus favoring transition state I.

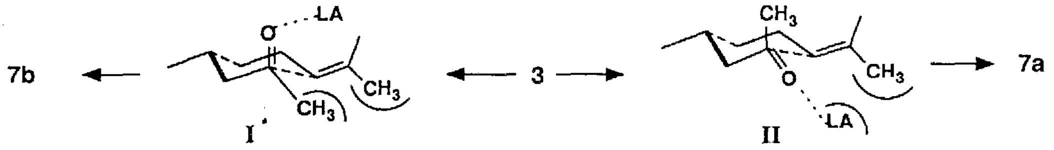


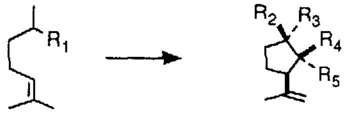
Figure 1. Proposed transition states for cyclization of methyl ketone **3**.

An analogous series of 5-ring precursors were also investigated (Table II). The cyclization of **9** in the presence of Me_2AlCl is a complex reaction, giving a variety of rearranged products depending on the reaction conditions.[2c] The SiO_2/high pressure promoted cyclization of **9** gave a superior yield of ene-like products **12**, however, product stereoselectivity was not high.

In contrast to the successful cyclization of **3**, methyl ketone **10** showed no evidence of cyclization, even under forcing SiO_2/high pressure conditions. The cyclization of **10** using $MeAlCl_2$ has been reported to give a rearranged cyclized product[2c] and a related trifluoromethyl ketone underwent the expected ene-like cyclization in the presence of $EtAlCl_2$.[12] The requirement of $RAlCl_2$ Lewis acids for the cyclization of δ,ϵ-unsaturated ketones is an indication that the Lewis acidity of SiO_2 at 15 kbar is less than that of $RAlCl_2$.

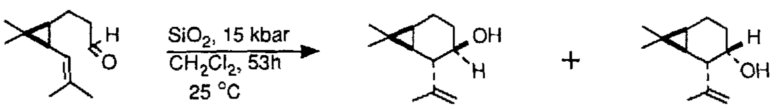
The SiO_2 induced cyclization of diester **11**[13,9] at 15 kbar gave a high yield of cyclized product **13** with good selectivity for the all *trans* isomer **13a**. In contrast to the facile $ZnBr_2$ catalyzed cyclization of **4**,[10] treatment of **11** with $ZnBr_2$[10c,14] gave a polymeric material that only contained traces of **13**.

Table II: 5-Ring Cyclizations Using Oven-dried Silica Gel at 15 kbar.



starting cmpd R_1	products	R_2	R_3	R_4	R_5	yield (%)	conditions
9: CHO	**12a**	CH_3	H	OH	H	14	SiO_2, CH_2Cl_2, 15 kbar, 48 h, 25 °C
	12b	H	CH_3	OH	H	26	9% unreacted **9** isolated
	12c	CH_3	H	H	OH	38	
10: COMe						no reaction	SiO_2, CH_2Cl_2, 15 kbar, 96 h, 80 °C
11: $CH=C(CO_2Me)_2$	**13a**	CH_3	H	H	$CH(CO_2Me)_2$	75	SiO_2, CH_2Cl_2, 15 kbar, 90 min, 25 °C
	13b	H	CH_3	$CH(CO_2Me)_2$	H	8	16% unreacted **10** isolated

The cyclization of **14**[15] to **15** was investigated as a model system for the C/D ring portion of phorbol.[16] The use of SiO_2 at 15 kbar proved to be an effective method of cyclization for this system, although the stereoselectivity about the new C-C bond was only 2:1. While the use of $ZnBr_2$ has been reported to be very effective for the cyclization of **1**,[17a,18] its use in the cyclization of **14** gave only traces of **15** along with complete decomposition of **14**. Unfortunately, the methyl ketone analog of **14** was completely stable to SiO_2 at 15 kbar, even after 96 h at 80 °C.



14 **15a** (56%) **15b** (29%)

While 7-endo[19] cyclizations appear to go readily using SiO_2 at 1 atm,[2a,b] the attempted SiO_2/high pressure promoted 7-exo cyclization pf homocitronellal,[20] the one-carbon homolog of **1** (R_1=CH_2CHO, R_2=CH_3), gave only decomposition along with recovered homocitronellal.

The examples above work equally well at 7 kbar, albeit reaction times must be increased. In addition, 1 atm control reactions were performed. Compounds **2**, **3**, **10** and **14** gave no reaction. Compounds **1** and **9** underwent partial conversion to **5** and **12**, however, the yield of cyclized material was <10% after 7 days. Unsaturated diesters **4** and **11** were more reactive, giving a 50% yield of **8** and **13** after 14 days at 1 atm in the presence of SiO_2. Exposure of **1**, **4**, **9**, and **11** to a pressure of 15 kbar in the absence of SiO_2 gave no reaction.

The present investigation has demonstrated that SiO_2 at high pressure is an effective catalytic system for promoting ene-like cyclizations and the yields and selectivities of cyclized products are comparable to those obtained using a variety of other conditions.[17,2,21] Certain limitations involving 5- and 7-membered ring precursors, disubstituted olefin acceptors, and α,β-unsaturated monocarbonyl compounds exist, however, this new method is generally applicable to a variety of unsaturated carbonyl systems. The effectiveness of SiO_2 at high pressure in promoting the cyclization of **11** and the sensitive vinyl cyclopropyl aldehyde **14** underscores the mildness of this new method.

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6 General Reaction Procedure: A CH_2Cl_2 (hexane, THF, and CH_3CN all gave significantly lower yields) solution of the substrate (1-1.5 M) was placed in an 8 mm diameter teflon tube, sealed at one end with a screw clamp. Silica gel[7] (1g/mL of solution) was quickly added, with stirring, to form a thick slurry. The tube was sealed, placed in the high pressure apparatus,[8a] and pressurized. Upon depressurization, the compacted silica gel mixture was broken up, extracted with CH_2Cl_2, and filtered. Evaporation of the solvent gave the crude products, which were separated by flash chromatography.[8b]

7 Initially, standard flash chromatography grade SiO_2 (230-400 mesh) was used as received, however, significant amounts (10-15%) of diol side products were obtained in the cyclizations of **1** and **9**. The diol products were formed by attack of water on a cyclization intermediate, and not by olefin hydration, since the desired cyclized products (**5**,**12**) were stable to the original reaction conditions. Simply heating the SiO_2 at 130 °C for 24 h prior to use removed sufficient water that diol formation was no longer observed.

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9 The α,β-unsaturated monoester analogs of **4** and **11** underwent *tran-cis* isomerization in the presence of SiO_2 at 15 kbar, but no cyclization products were observed.

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13 **11**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.81 (d,1,*J*=10.9 Hz), 5.05 (m,1), 3.81 (s,3), 3.77 (s,3), 2.55 (m,1), 1.92 (m,2), 1.66 (s,3), 1.57 (s,3), 1.4 (m,2), 1.05 (d,3,*J*=6.6 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 165.67, 164.15, 154.78, 131.69, 126.52, 123.50, 51.95, 51.81, 36.28, 34.19, 25.56, 25.38, 19.52, 17.38. **13a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (s br,2), 3.67 (s,3), 3.64 (s,3), 3.39 (d,1,*J*=6.7 Hz), 2.51 (ddd,1,*J*=9.1,9.1,8.6 Hz), 2.05 (ddd,1,*J*=9.4, 9.1,6.7 Hz), 1.89 (m,1), 1.75 (m,2), 1.65 (s,3), 1.55 (m,1), 1.27 (m,1), 0.97 (d,3,*J*=6.7 Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 169.14, 146.44, 111.10, 53.94, 52.00, 51.86, 51.79, 48.93, 37.57, 33.31, 29.86, 20.40, 18.46. **13b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (m, 1), 3.68 (s, 3), 3.62 (s,3), 3.26 (d,1,*J*=10.6 Hz), 2.79 (q,1,*J*=7.7 Hz), 2.4 (ddd,1,*J*=10.6,7.6,6.3 Hz), 1.9 (m,2), 1.75 (m,1), 1.67 (s br,3), 1.62 (m,1), 1.19 (m,1), 0.93 (d,3,*J*=6.5 Hz).

14 The 5-methyl analog of **10** has been reported to undergo facile cyclization in the presence of $ZnBr_2$. See: Sarkar, T. K.; Subba Rao, P. S. V. *Synth. Commun.* **1989**, *19*, 1281.

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